CLAIMS

We claim:

1. A method for designing an inhibitor of a second serine/threonine kinase or a second tyrosine kinase comprising the steps of:

a. identifying amino acids in an ATP binding site of a first serine/threonine kinase or a first tyrosine kinase which form close contacts with a compound bound to said ATP binding site;

b. employing protein alignment means to identify a second serine/threonine kinase or a second tyrosine kinase that form some, but not all, of the close contacts formed between said compound and said first serine/threonine kinase or said first tyrosine kinase;

c. altering an amino acid in the ATP binding site of said second serine/threonine kinase or said second tyrosine kinase to create a mutant second serine/threonine kinase or a mutant second tyrosine kinase, wherein said compound binds with at least 10-fold greater affinity to said mutant second kinase than to said second kinase;

d. confirming ~~that~~ said compound binds with greater affinity to said mutant second serine/threonine kinase or said mutant second tyrosine kinase than to said second serine/threonine kinase or said second tyrosine kinase; and

e. using molecular modeling means to modify said compound to create an inhibitor of said second kinase, such that said inhibitor binds to said second kinase with at least 10-fold greater affinity than said compound binds to said second kinase.

2. The method according to claim 1, wherein said first serine/threonine kinase or tyrosine kinase and said second serine/threonine kinase or tyrosine kinase are both MAP kinases.

3. The method according to claim 2, wherein said first serine/threonine kinase or tyrosine kinase is p38 having the amino acid sequence set forth in SEQ ID NO:1.

4. The method according to claim 3, wherein said compound is a pyridinyl-imidazole inhibitor of p38.

5. The method according to claim 4, wherein said compound is selected from SB203580 or SB202190.

6. The method according to claim 2, wherein said second serine/threonine kinase or tyrosine kinase is selected from:

a. ERK2 having the amino acid sequence set forth in SEQ ID NO:2, wherein amino acid 103 is isoleucine, amino acid 105 is glutamine, amino acid 106 is aspartic acid, amino acid 109 is glutamic acid and amino acid 110 is threonine; or

b. JNK3 comprising amino acids 40-402 of SEQ ID NO:3, wherein amino acid 146 is methionine and amino acid 150 is aspartic acid.

7. The method according to claim 6, wherein

a. when said second kinase is ERK2, said mutant second kinase is an ERK-2 mutant having an amino acid sequence as set forth in SEQ ID NO:2, wherein amino

acid 105 is threonine or alanine; or

b. wherein said second kinase is JNK3, said mutant second kinase is a JNK3 mutant comprising amino acids 40-402 of SEQ ID NO:3, wherein amino acid 146 is alanine or threonine.

8. The method according to claim 7, wherein in SEQ ID NO:2 amino acid 103 is leucine, amino acid 106 is histidine, amino acid 109 is glycine and amino acid 110 is alanine.

9. The method according to claim 7, wherein in SEQ ID NO:3 amino acid 150 is glycine.

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10. A mutant second serine/threonine kinase or tyrosine kinase characterized by:

a. at least one amino acid substitution in an ATP binding site as compared to a corresponding naturally occurring second kinase;

b. the ability to bind with a K_i or a K_d of less than 10 μM a compound that binds to an ATP binding site of a first serine/threonine kinase or tyrosine kinase; and

c. the ability to bind said compound with at least a 10-fold lower K_i or K_d than the K_i or K_d for said compound with said second kinase.

11. The mutant second kinase according to claim 10, wherein said first and said second kinases are MAP kinases.

12. The mutant second kinase according to claim 11, wherein said mutant second kinase is selected

from:

a. a mutant ERK2 consisting of the amino acid sequence as set forth in SEQ ID NO:2, wherein amino acid 105 is threonine or alanine; or

b. a mutant JNK3 comprising amino acids 40-402 of SEQ ID NO:3, wherein amino acid 146 is threonine or alanine.

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13. The mutant second kinase according to claim 12, wherein in SEQ ID NO:2 amino acid 103 is leucine, amino acid 106 is histidine, amino acid 109 is glycine and amino acid 110 is alanine.

14. The mutant second kinase according to claim 12, wherein in SEQ ID NO:3 amino acid 150 is glycine.

15. A crystallizable co-complex of a mutant second kinase according to any of claims 10 to 14 and an inhibitor of said first kinase bound to the ATP binding site of said mutant second kinase.

16. The crystallizable co-complex according to claim 13, wherein said first kinase is p38, said second kinase is a MAP kinase and said inhibitor is a pyridinyl-imidazole inhibitor of p38.

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17. The co-complex according to claim 13, wherein said pyridinyl-imidazole inhibitor of p38 is selected from SB203580 or SB202190.

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